



# TRANSMITTAL FORM

Be used for all correspondence after initial filing)

Total Number of Pages in This Submission	13	Application Number	10/701,186
		Filing Date	November 4, 2003
		First Named Inventor	Joseph L. Duffy, et al
		Art Unit	1626
		Examiner Name	Laura L. Stockton
		Attorney Docket Number	21167

## ENCLOSURES (Check all that apply)

<input type="checkbox"/> Fee Transmittal Form <input type="checkbox"/> Fee Attached <input type="checkbox"/> Amendment/Reply <input type="checkbox"/> After Final <input type="checkbox"/> Affidavits/declaration(s) <input type="checkbox"/> Extension of Time Request <input type="checkbox"/> Express Abandonment Request <input type="checkbox"/> Information Disclosure Statement <input type="checkbox"/> Certified Copy of Priority Document(s) <input type="checkbox"/> Response to Missing Parts/Incomplete Application <input type="checkbox"/> Response to Missing Parts under 37 CFR 1.52 or 1.53	<input type="checkbox"/> Drawing(s) <input type="checkbox"/> Licensing-related Papers <input type="checkbox"/> Petition <input type="checkbox"/> Petition to Convert to a Provisional Application <input type="checkbox"/> Power of Attorney, Revocation Change of Correspondence Address <input type="checkbox"/> Terminal Disclaimer <input type="checkbox"/> Request for Refund <input type="checkbox"/> CD, Number of CD(s) _____	<input type="checkbox"/> After Allowance Communication to Technology Center (TC) <input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences <input checked="" type="checkbox"/> Appeal Communication to TC (Appeal Notice, Brief, Reply Brief) <input type="checkbox"/> Proprietary Information <input type="checkbox"/> Status Letter <input type="checkbox"/> Other Enclosure(s) (please Identify below):
<b>Remarks</b> Amended Brief on Appeal submitted in Response to Notice dated August 17, 2006.		

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Name	Richard C. Billups	Registration No. (Attorney/Agent)	31,916
Signature		Date	9/15/06

## CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450 on this date: September 15, 2006

Typed or printed name	Pamela Spalding		
Signature		Date	9-15-06



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
BOARD OF PATENT APPEALS AND INTERFERENCES

Applicants: Joseph L. Duffy, et al.

Serial No: 10/701,186

Filed: November 4, 2003

Customer No: 000210

Confirmation No: 6239

Case No.: 21167

Art Unit: 1626

For: CYANTHIOPHENE DERIVATIVES,  
COMPOSITIONS CONTAINING COMPOUNDS  
AND METHODS OF USE

Examiner:

Laura L. Stockton

Mail Stop Appeal Brief - Patents  
Commissioner for Patents  
P. O. Box 1450  
Alexandria, VA 22313-1450

APPELLANTS' BRIEF ON APPEAL

Sir:

This is an appeal pursuant to 35 U.S.C. § 134 and 37 C.F.R. §§ 41.31 et seq. from the final rejection of claims 14 and 15 mailed on March 6, 2006 in the above identified patent application. Claims 14 and 15 were rejected twice. This Brief is in furtherance of the Notice of Appeal filed in this case on May 22, 2006. Accordingly this brief is timely filed. This brief is submitted in triplicate. The fee for submitting this brief is \$500.00 (37 C.F.R. 1.17(c)), and has already been charged to our deposit account. Please charge Deposit Account No. 13-2755 in the amount of \$500.00 to cover this fee. The Commissioner is hereby authorized to charge any additional fees that may be required for this appeal or to make this brief timely, or credit any overpayment to Deposit Account No. 13-2755.

**I hereby certify that this correspondence is being  
deposited with the United States Postal Service as  
first class mail in an envelope addressed to:  
Commissioner for Patents, P.O. Box 1450,  
Alexandria, Virginia 22313-1450, on the date  
appearing below.**

**MERCK & CO., INC.**

*Pamela Sealing* Date 9-15-06

Serial. No.: 10/701,186  
Filing Date: November 4, 2003  
Case No.: 21167  
Page No.: 2

## **TABLE OF CONTENTS**

- I. Real Party in Interest
- II. Related Appeals and Interference
- III. Status of Claims
- IV. Status of Amendments
- V. Summary of Claimed Subject Matter
- VI. Concise Explanation of Independent Claims
- VII. Concise Statement of Each Ground of Rejection of Appeal
- VIII. Grounds of Rejection to be Reviewed on Appeal
- IX. Grouping of Claims
- X. Argument
- XI. Conclusion
- XII. Claims Appendix

## **I Real Party in Interest**

The real party in interest in this appeal is Merck & Co., Inc. a corporation of the state of New Jersey, and the assignee of the captioned patent application.

## **II Related Appeals and Interferences**

There are no appeals or interferences known to Appellant, his legal representative, or the assignee that will directly affect, will be directly affected by or will have a bearing on the Board's decision in this appeal.

## **III Status of Claims**

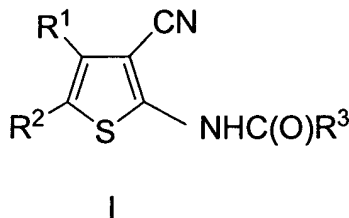
Claims 14, 15, 16, 19 and 20 are presently in the case. Claims 14 and 15 stand finally rejected under 35 U.S.C. §103(a) as obvious in view of Kawai et al, U.S. Patent No. 6,048,880 (Kawai). Claims 16, 19 and 20 were deemed allowable by the Examiner. Appellants hereby appeal the final rejection of claims 14 and 15.

## **IV Status of Amendments**

There were no amendments filed subsequent to the final rejection dated March 6, 2006. Therefore the claims set forth in Appendix A to this brief are those set forth before the final rejection.

## **V Summary of Claimed Subject Matter**

Appellants' invention as presently claimed relates to compounds of formula I:



The compounds are 3-cyanothiophenes having an amide attached through a nitrogen atom at position two of the thiophene ring. The compounds are pharmacologically active as glucagon receptor antagonists and are therefore expected to be useful for the treatment of type 2 diabetes.

## **VI Concise Explanation of Independent Claims**

Pursuant to 37 C.F.R. 41.37 ( c ) (1)(v), Appellants note that claim 14 and 15 are independent claims.

Claim 14 addresses 3-substituted cyanothiophenes wherein R<sup>1</sup> represents methyl at position 4 (Specification at page 8, Line 2). A 3-pentyl group is attached to the thiophene nucleus at position 2 through an amide linker (specification at page 8, line 3) and a variety of side groups represented by R<sup>2</sup> can be found at position 5 (specification at page 8, line 4 – page 10, line 1). This is a subset of claim 1 as originally presented, and is fully supported by the specification (specification at page 7, line 35 through page 10, line 2).

Claim 15 addresses a subset of compounds of original claim 1 (specification at page 10, line 3 – page 11, line 29). The compounds recited in this claim are also the subject of the written examples (specification at page 28, line 22 – page 53, line 2).

## **VII Concise Statement of each Ground of Rejection of Appeal**

Claims 14 and 15 were finally rejected under 35 U.S.C. 103 (a) for obviousness over Kawai et al (U.S. Patent No. 6,048,880).

## **VIII Grounds of Rejection to be Reviewed on Appeal**

Whether claims 14 and 15 are patentable under 35 U.S.C. § 103 (a).

## **IX Grouping of Claims**

Claims 14 and 15 presently on appeal stand or fall together.

## **X Argument**

As Appellants discuss in detail below, the final rejection of claim 14 and 15 is factually unsupported by the single reference relied up, Kawai. It is therefore submitted that the rejection does not meet the burden of presenting a prima facie case of obviousness and therefore unpatentability. For this reason alone, Appellants are entitled to the grant of a patent. In re Oetiker 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

To make out a case of prima facie obviousness, the Examiner must determine that in view of the scope and content of the prior art, the difference between the art and the claims and the level of skill in the art, a reference would at least appear to render the claimed invention obvious to one of ordinary skill. Here, the reference relied upon does not satisfy this requirement.

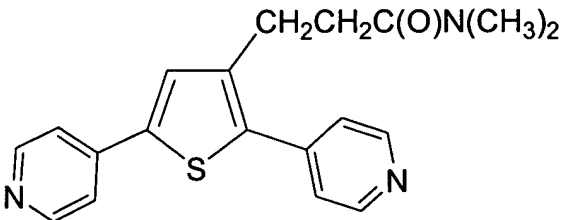
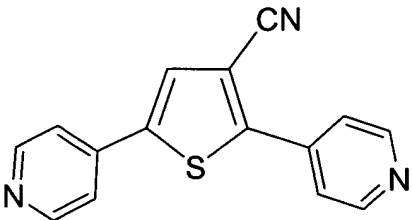
### **Structural Differences**

The prior art reference relied upon by the Examiner provides a broad genus that would not have led one of ordinary skill in the direction that Appellants have taken. First, the central ring in the Kawai reference is highly variable. It can represent a furan (X in Kawai represents an oxygen atom), a thiophene (X represents sulfur), or an oxidized form of thiophene (X represents a sulfoxyl or sulfonyl group). Moreover, the central ring in Kawai can be fused to a second ring (two of R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> in Kawai are taken together and form a group of the formula -A<sup>1</sup>-B<sup>1</sup>-A<sup>2</sup>- or -A<sup>1</sup>-B<sup>1</sup>-A<sup>3</sup>-B<sup>2</sup>-A<sup>2</sup>-, which together with the carbon atoms to which A<sup>1</sup> and A<sup>2</sup> are attached, defines an additional fused ring having 4 to 8 ring atoms, with this ring being further optionally substituted.

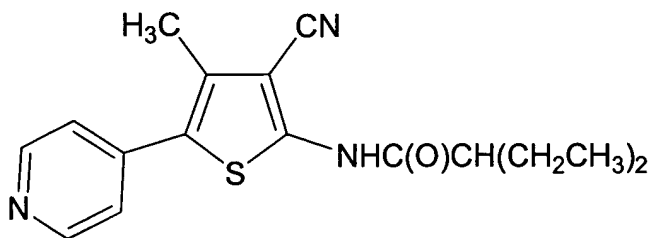
The preferred groups described in Columns 7 and 8 of Kawai include furan and thiophene compounds where the central furan or thiophene ring is optionally fused to a second ring. No preference is specified in Kawai for thiophene compounds.

Kawai further requires the presence of a 4-pyridyl group attached to the central aromatic heterocyclic ring, either furan, thiophene, sulfoxyl or a sulfonyl containing ring, at position 2, and is varied at other points of substitution around the ring.

In the final rejection, the Examiner identified the following compounds from Kawai in support of the position that the claims are prima facie obvious in view of Kawai:

Example 49 of Kawai	Col. 9, line 19 of Kawai
	

In claim 14 presently on appeal, the following compound is disclosed:



The other compounds in the appeal claims are structurally more distant from the compounds of Kawai than the compound shown above.

Nothing within Kawai or any other reference would have taught or would have appeared to suggest to the ordinarily skilled artisan to delete one of the two pyridyl rings shown in Example 49 or Col. 9, line 19 of Kawai, to reverse the linkage to the thiophene such that the alkyl chain is linked to the thiophene through the amide nitrogen atom instead of a carbon atom, or to replace the dimethylpropionamide group found in the compound of example 49 with a cyano group, and to place a 3-pentyl group at position 2 of the central thiophene ring linked through an amide moiety.

The structural differences between Appellants' claimed invention and the Kawai reference are therefore urged to be clear and in favor of a finding that no prima facie obviousness exists with respect to claims 14 and 15.

The Examiner has urged that Kawai teach thiophene compounds that are structurally similar to the instantly claimed compounds, and that the instantly claimed compounds are generically described in

Kawai. The selection of  $-\text{CN}$ ,  $\text{R}^1$  representing  $\text{CH}_3$ , and  $\text{R}^3$  representing 3-pentyl positioned as recited in claim 14 on a thiophene central ring does not constitute an “indiscriminate” selection of “some among many” substituent groups, as described in In re Lemin 141 U.S.P.Q. 814 (CCPA 1964). In Lemin, the claims were allowed because the choice of a specified number of total carbon atoms was critical and imparted a special significance to the compounds, i.e., the compounds that were claimed were selective and potent herbicides. Lemin successfully demonstrated that absent the critical number of carbon atoms, greater than 5, the compounds exhibited no significant herbicidal activity against crabgrass.

#### **Differences in Properties**

In the present case, there are distinctly different and unexpected properties embodied in the compounds of the claims relative to Kawai. Yet, the Examiner has alleged that the existence of the genus of Kawai would render the species claimed *prima facie* obvious, and that one of ordinary skill would have been motivated by virtue of similar activities (cytokine production inhibitor).

The Kawai compounds are alleged to be useful as inhibitors of the production of inflammatory cytokines, such as  $\text{TNF-}\alpha$  and  $\text{IL-1}\beta$ , and are therefore allegedly useful to treat inflammatory disorders.

The compounds that are claimed by Appellants have a distinctly different activity, functioning as glucagon receptor antagonists. Appellants dispute that the claimed compounds and the Kawai reference therefore disclose compounds which would “possess similar activity” as alleged by the Examiner. Inhibiting cytokine production is not similar to antagonizing the glucagon receptor, when evaluated from the perspective of one ordinarily skilled in the art.

Moreover, a perceived similarity between utilities does not negate unexpectedness in the property discovered. The glucagon receptor antagonist activity discovered could in fact be very similar to the alleged utility disclosed in Kawai and still qualify as a property which is unexpected in view of Kawai. Nothing within Kawai (or any other reference) would have negated unexpectedness in the glucagon receptor antagonist property. Hence, *prima facie* obviousness based upon similar activities does not exist.



Serial. No.: 10/701,186  
Filing Date: November 4, 2003  
Case No.: 21167  
Page No.: 8

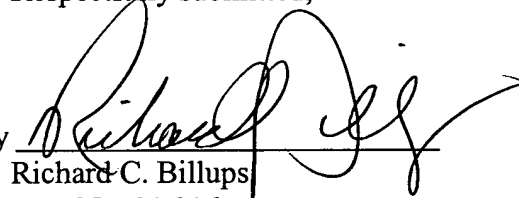
It is well known that a chemical compound is comprised of its structure and the properties embodied therein; the two cannot be separated. In re Papesh 137 U.S.P.Q. 43 (CCPA 1963). The structural differences taken in combination with the difference in activities does not support a case of prima facie obviousness. For the above reasons, Appellants respectfully submit that the final rejection of claim 14 and 15 is in error and should be reversed.

XI. Conclusion

In conclusion, Appellants respectfully submit that the final rejection of claims 14 and 15 is in error and should be reversed.

Respectfully submitted,

By



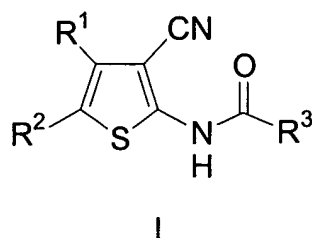
Richard C. Billups  
Reg. No. 31,916  
Attorney for Applicants  
Merck & Co., Inc.  
P.O. Box 2000  
Rahway, NJ 07065-0907  
(732) 594-4683

Date: 9/15/06

## XII. Claims Appendix

### Appendix A

Claim 14. A compound of the formula I:

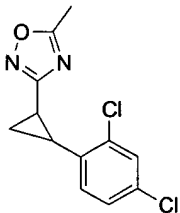
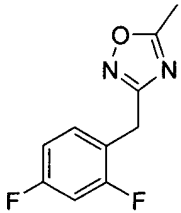
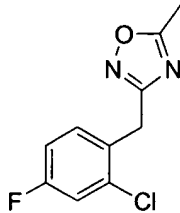
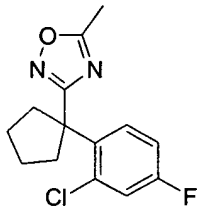
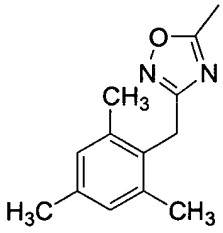
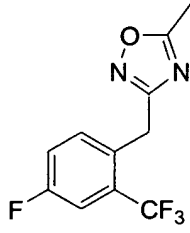
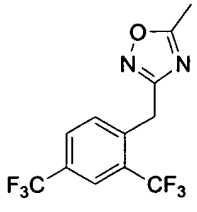
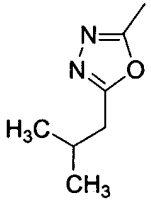
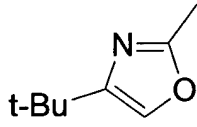
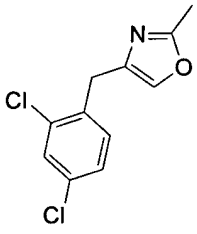
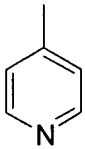
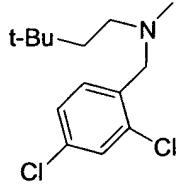
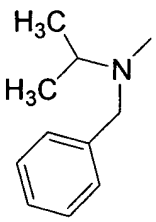
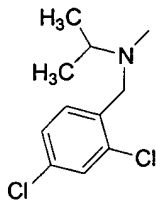
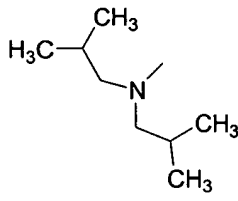


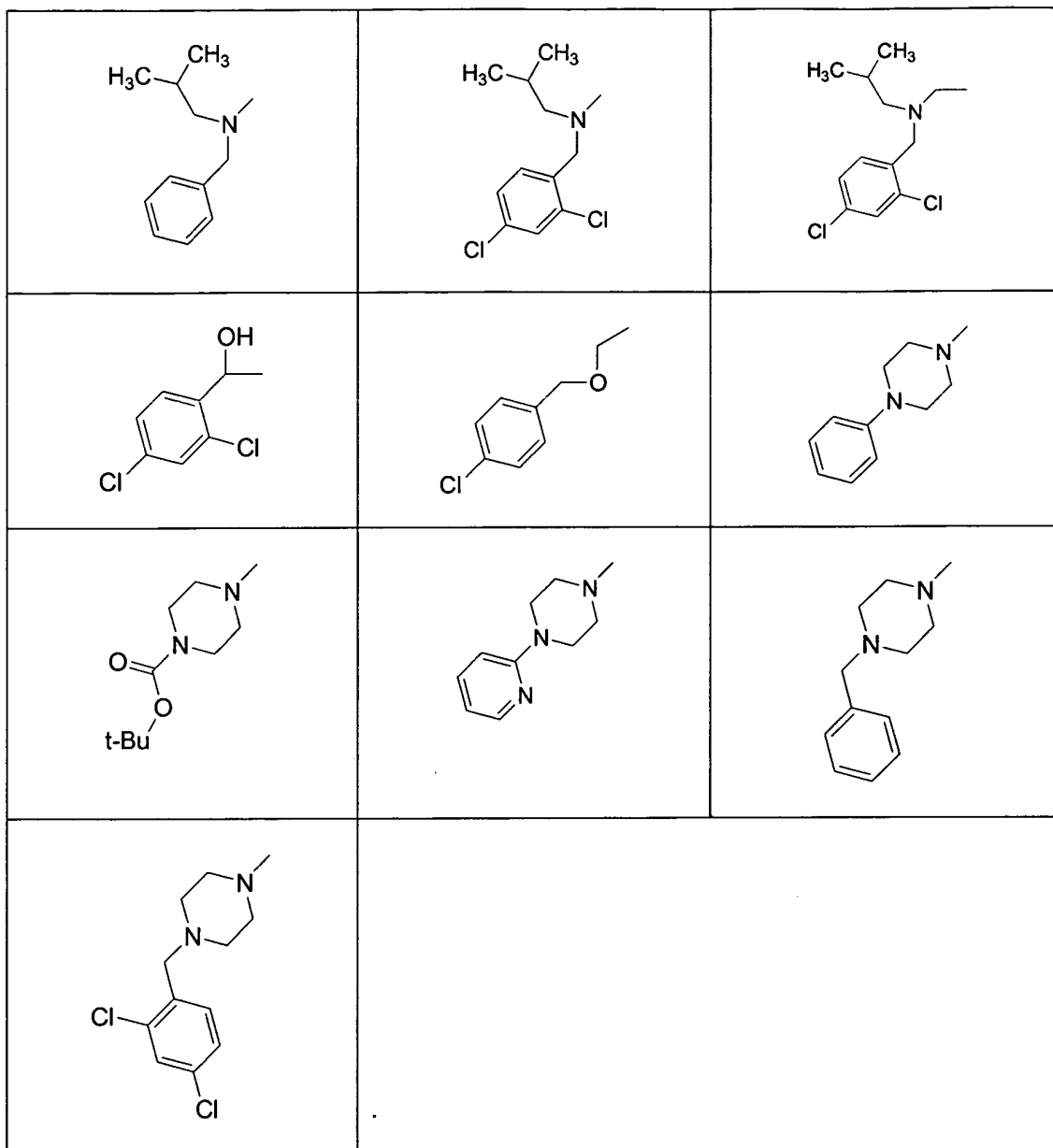
wherein:

R<sup>1</sup> represents methyl;

R<sup>3</sup> represents 3-pentyl, and R<sup>2</sup> is selected from the table below:

R <sup>2</sup>		



Claim 15. A compound selected from the group consisting of:

- N-[3-cyano-5-(3-isobutyl-1,2,4-oxadiazol-5-yl)-4-methylthien-2-yl]-2-ethylbutanamide;
- N-{3-cyano-5-[3-(2,4-dichlorobenzyl)-1,2,4-oxadiazol-5-yl]-4-methylthien-2-yl}-2-ethylbutanamide;
- N-[5-(3-tert-butyl-1,2,4-oxadiazol-5-yl)-3-cyano-4-methylthien-2-yl]-2-ethylbutanamide;
- N-[5-(3-benzyl-1,2,4-oxadiazol-5-yl)-3-cyano-4-methylthien-2-yl]-2-ethylbutanamide;
- N-[3-cyano-4-methyl-5-(3-phenyl-1,2,4-oxadiazol-5-yl)thien-2-yl]-2-ethylbutanamide;

N-[3-cyano-4-methyl-5-(3-pyridin-2-yl-1,2,4-oxadiazol-5-yl)thien-2-yl]-2-ethylbutanamide;  
 N-[3-cyano-4-methyl-5-(3-pyridin-3-yl-1,2,4-oxadiazol-5-yl)thien-2-yl]-2-ethylbutanamide;  
 N-[3-cyano-4-methyl-5-(3-pyridin-4-yl-1,2,4-oxadiazol-5-yl)thien-2-yl]-2-ethylbutanamide;  
 N-{3-cyano-5-[3-(cyclohexylmethyl)-1,2,4-oxadiazol-5-yl]-4-methylthien-2-yl}-2-ethylbutanamide;  
 N-(3-cyano-5-{3-[1-(2,4-dichlorophenyl)cyclopropyl]-1,2,4-oxadiazol-5-yl}-4-methylthien-2-yl)-2-ethylbutanamide;  
 N-{3-cyano-5-[3-(2,4-difluorobenzyl)-1,2,4-oxadiazol-5-yl]-4-methylthien-2-yl}-2-ethylbutanamide;  
 N-{5-[3-(2-chloro-4-fluorobenzyl)-1,2,4-oxadiazol-5-yl]-3-cyano-4-methylthien-2-yl}-2-ethylbutanamide;  
 N-(5-{3-[1-(2-chloro-4-fluorophenyl)cyclopentyl]-1,2,4-oxadiazol-5-yl}-3-cyano-4-methylthien-2-yl)-2-ethylbutanamide;  
 N-{3-cyano-5-[3-(mesitylmethyl)-1,2,4-oxadiazol-5-yl]-4-methylthien-2-yl}-2-ethylbutanamide;  
 N-(3-cyano-5-{3-[4-fluoro-2-(trifluoromethyl)benzyl]-1,2,4-oxadiazol-5-yl}-4-methylthien-2-yl)-2-ethylbutanamide;  
 N-(5-{3-[2,4-bis(trifluoromethyl)benzyl]-1,2,4-oxadiazol-5-yl}-3-cyano-4-methylthien-2-yl)-2-ethylbutanamide;  
 N-[3-cyano-5-(5-isobutyl-1,3,4-oxadiazol-2-yl)-4-methylthien-2-yl]-2-ethylbutanamide;  
 N-[5-(4-tert-butyl-1,3-oxazol-2-yl)-3-cyano-4-methylthien-2-yl]-2-ethylbutanamide;  
 N-{3-cyano-5-[4-(2,4-dichlorobenzyl)-1,3-oxazol-2-yl]-4-methylthien-2-yl}-2-ethylbutanamide;  
 N-(3-cyano-4-methyl-5-pyridin-4-ylthien-2-yl)-2-ethylbutanamide;  
 N-{3-cyano-5-[(2,4-dichlorobenzyl)(3,3-dimethylbutyl)amino]-4-methylthien-2-yl}-2-ethylbutanamide;  
 N-{5-[benzyl(isopropyl)amino]-3-cyano-4-methylthien-2-yl}-2-ethylbutanamide;  
 N-{3-cyano-5-[(2,4-dichlorobenzyl)(isopropyl)amino]-4-methylthien-2-yl}-2-ethylbutanamide;  
 N-[3-cyano-5-(diisobutylamino)-4-methylthien-2-yl]-2-ethylbutanamide;  
 N-{5-[benzyl(isobutyl)amino]-3-cyano-4-methylthien-2-yl}-2-ethylbutanamide;  
 N-{3-cyano-5-[(2,4-dichlorobenzyl)(isobutyl)amino]-4-methylthien-2-yl}-2-ethylbutanamide;  
 N-{3-cyano-5-[(2,4-dichlorophenyl)(hydroxy)methyl]-4-methylthien-2-yl}-2-ethylbutanamide;  
 N-(3-cyano-5-{[(2,4-dichlorobenzyl)(isobutyl)amino]methyl}-4-methylthien-2-yl)-2-ethylbutanamide;  
 N-[3-cyano-4-methyl-5-(4-phenylpiperazin-1-yl)thien-2-yl]-2-ethylbutanamide;  
 tert-butyl 4-{4-cyano-5-[(2-ethylbutanoyl)amino]-3-methylthien-2-yl}piperazine-1-carboxylate;

Serial. No.: 10/701,186  
Filing Date: November 4, 2003  
Case No.: 21167  
Page No.: 13

N-[3-cyano-4-methyl-5-(4-pyridin-2-ylpiperazin-1-yl)thien-2-yl]-2-ethylbutanamide;  
N-[5-(4-benzylpiperazin-1-yl)-3-cyano-4-methylthien-2-yl]-2-ethylbutanamide;  
N-{3-cyano-5-[4-(2,4-dichlorobenzyl)piperazin-1-yl]-4-methylthien-2-yl}-2-ethylbutanamide; and  
N-(5-[[4-chlorobenzyl]oxy]methyl)-3-cyano-4-methylthien-2-yl)-2-ethylbutanamide, as well as the  
pharmaceutically acceptable salts and solvates thereof.